

Topical Delivery Enhancement with Multilamellar Liposomes into Pilosebaceous Units: I. In Vitro Evaluation Using Fluorescent Techniques with the Hamster Ear Model

Linda M. Lieb, Chandrasekharan Ramachandran, Kamel Egbaria, and Norman Weiner

College of Pharmacy, The University of Michigan, Ann Arbor, Michigan, U.S.A.

Evidence suggesting liposomal delivery into the pilosebaceous unit of the male Syrian hamster ear membrane was found using two fluorescent techniques, quantitative fluorescence microscopy (QFM), and a scraping method where the various tissue strata of treated skin are analyzed using fluorescence spectrophotometry.

Whole ears were mounted on Franz diffusion cells and treated for 24 h with 40 μ l of the following test formulations, each containing $\approx 100 \mu\text{g/ml}$ carboxyfluorescein (CF): i) multilamellar phosphatidylcholine:cholesterol:phosphatidylserine liposomes; ii) HEPES buffer (pH, 7.4); iii) 5%

propylene glycol; iv) 10% ethanol; v) 0.05% sodium lauryl sulfate; and vi) a suspension of the same lipids used to form the liposomes that were not processed so as to produce a bilayer configuration. Topical application of the liposomally based formulation resulted in a significantly higher accumulation of CF in the pilosebaceous units than the application of any of the other non-liposomal formulations. There was excellent correlation between the two analytical methods used to determine CF deposition into the sebaceous glands. *J Invest Dermatol* 99:108–113, 1992

There is a renewed interest in the importance of appendages, particularly the follicular route, in the topical delivery of medicaments. Ille et al [1] recently reported that in vitro percutaneous steady-state flux for representative penetrants were 2–4 times higher in normal, hairless rat skin (follicular density 100–200/cm²) relative to their developed appendage-free model [2]. The importance of the follicular route was confirmed with a second animal model for (³H)hydrocortisone penetration when follicle-free newborn rat skin was compared to fully developed appendaged 5-d-old postnatal rat skin. For this model, differences in steady-state flux and 24-h diffusion values favored appendaged skin by a factor of about five.

Pitman and Rostas [3] reported in vitro penetration of levamisole from an organic solvent to be 400 times greater for cattle skin as compared to human skin harvested either from upper thigh or breast. They claimed the differences were at least partly due to large

differences in follicular density [$\sim 2000/\text{cm}^2$ [4] for cattle skin versus 55/cm² for human thigh [5,6]].

Feldmann and Maibach [7] and Maibach et al [8] noted in vivo absorption in the compounds tested depended upon the regional differences in the morphology of human skin used. Absorption was increased in areas of increased follicular density and size, e.g., forehead and scalp.

Whalberg [9] performed one of the first in vivo comparison experiments of hairy and non-hairy skin in a guinea pig model. Use was made of the bald dorsal ear for comparison to presumably macroscopically similar, albeit densely appendaged, heavy coat in the back. NaCl and HgCl₂ were employed as test substances in various concentrations with distilled water and 1% alkyl aryl sulfonate as vehicles. In vitro absorption through the hairy skin was higher, irrespective of the permeant or vehicle used. However, the importance of the follicular route was less clear for the in vivo studies, where the relative importance of the follicular and transepidermal routes were dependent on the permeant tested.

Many qualitative experiments have been reported supporting the pilosebaceous route as a viable means of delivering substances. Shelley and Melton [10] noted the appearance of multiperifollicular tiny wheals as a pharmacologic response upon application of epinephrine and histamine phosphate to human subjects. They claimed further substantiation of follicular delivery by the observation that the greatest absorption occurred in the hairier areas of the body. They reported the acceleration of this response from histamine depended upon various factors, such as vehicle used, drug concentration, chemical structure of permeant, and location of induction site, the most important factor being the penetrating vehicle used [11]. Mackee [12], in a comparison study performed between vehicle types using histochemical techniques and the guinea pig model reported that the highest pilosebaceous penetration occurred with vehicles that were "mixtures of various solvents, interface active agents, coupling agents and solubilizers."

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Reprint requests to: Dr. Norman Weiner, College of Pharmacy, The University of Michigan, Ann Arbor, MI 48109-1065.

Abbreviations:

- CF: carboxyfluorescein
- CH: cholesterol
- ETOH: ethanol
- HEPES: (2-hydroxyethyl) piperazine-N'-(2-ethanesulfonic acid)
- MLV: multilamellar liposomes
- PC: phosphatidylcholine
- PG: propylene glycol
- PS: phosphatidylserine
- QFM: quantitative fluorescence microscopy
- SLS: sodium lauryl sulfate

Over the years, a number of reports have appeared in the literature suggesting significant amounts of penetrant in the pilosebaceous apparatus. These studies [13–17] relied on histoautoradiographic or autoradiographic techniques and the conclusions drawn by these techniques are often difficult to interpret. Almost a quarter of a century ago, Scheuplein [18–22] elaborated on the significance of the shunt pathway. He discussed the importance of this route for the percutaneous absorption of lipid-soluble, larger molecular volume substances such as steroids [21] as well as highly polar substances that penetrate the stratum corneum slowly and with difficulty [22]. There are many examples in the literature of a shunt or parallel diffusion pathway included in the mathematical modeling of percutaneous absorption. Corroller [23] discusses sebaceous accumulation and its mathematical treatment and some investigators [24,25] have developed shunt pathway compartmental models.

This report will present evidence of pilosebaceous delivery of carboxyfluorescein (a fluorescent marker) and topical delivery enhancement via the follicular route through the use of liposomal formulations. Syrian hamster ear as the model that emphasizes the follicular route was utilized for its anatomical and physiologic similarity to human pilosebaceous units [26]. Two quantitative fluorescent detection techniques were used to determine the effects of formulation on topical delivery of CF via the follicular route.

MATERIALS AND METHODS

Materials Chromatographically purified carboxyfluorescein (CF) was purchased from Molecular Probes, Inc. (Eugene, OR). CF is a very convenient aqueous marker for this study because fluorescent detection techniques have previously been used [27–31] for histologic observation of topical delivery of fluorescent dyes from conventional formulations into the pilosebaceous canal and sebaceous glands. Phosphatidylcholine (PC) and phosphatidylserine (PS) were obtained from Avanti Polar Lipids, Inc. (Birmingham, AL). *d*- α -tocopherol was purchased from Kodak (Rochester, NY). Cholesterol (CH) and (2-hydroxyethyl) piperazine-*N'*-(2-ethanesulfonic acid) (HEPES) were purchased from Sigma (St. Louis, MO). Gel Mount slide fixative was purchased from Biomedica Corp. (Foster City, CA). All other chemicals were from Fischer Scientific (Springfield, NJ).

Preparation of CF-Containing Formulations Multilamellar liposomes (MLV) containing PC:CH:PS at a mole ratio of 1:0.5:0.1 were prepared using the conventional film method [32]. Briefly, hydration of the lipid film was carried out using 100 μ g/ml CF solutions in 0.05 M isotonic HEPES buffer, pH 7.4, at a temperature of 30°C. The CF-containing liposomes were annealed at 30°C for 45 min and stored at 4°C overnight before use. The resultant liposomes contained ~10% entrapped CF and ~90% free CF as determined by size exclusion chromatography on Sephadex LX-20. No attempt was made to separate the free and entrapped marker. The total lipid concentration was 30 mg/ml. Additionally, the following vehicles were used to prepare formulations, all containing ~100 μ g/ml CF: i) HEPES buffer (pH, 7.4); ii) 5% PG in HEPES; iii) 10% ethanol in HEPES; iv) 0.05% SLS in HEPES; and v) a suspension of the same lipids used to form the liposomes that were not processed to produce a bilayer configuration.

In Vitro Diffusion Studies Franz diffusion cells having a diameter of 5 mm, a surface area of about 0.20 cm² and a 4-ml receiver compartment capacity, purchased from Crown Glass (Somerville, NJ), were used for these studies. Syrian golden hamsters, 10–14 weeks of age, purchased from Harlan-Sprague Dawley (Indianapolis, IN), were maintained at a photoperiod of 14 h of light and 10 h of darkness to maximize the androgen-dependent sebaceous-gland activity [26,33] and thus control their size. Food and water were provided ad libitum. Male Syrian hamster ear is the model of choice because its pilosebaceous units have anatomical and physiologic similarity to human skin [26]. The follicular density of hamster ear (~1000 follicles/cm²) is similar to that of the scalp (~800 follicles/cm²) and face (~770 follicles/cm²) of human male skin [5,6,34].

The hamsters were sacrificed and the ears obtained by cutting at the base. The whole ear was mounted, ventral side up with the medial section exposed to treatment, on the Franz diffusion cells and the receiver compartment filled almost completely with the buffer, leaving a small meniscus under the membrane (dorsal) of the receiver compartment. Preliminary studies revealed the importance of allowing realistic mimicking of the dehydration process when a formulation is applied to the skin in the clinical situation. This methodology allows the liposomal dispersion to form a patch on the skin while still leaving the membrane itself pliable and hydrated.

The cells were attached to a heater block and maintained at a temperature of 38°C to provide a membrane temperature of 32°C as verified with a temperature probe. Forty microliters of the test formulation were then applied to the donor side and the entire cell was shielded from light by wrapping it with aluminum foil. The foil wrapping was loose enough so that the experiments were still conducted under non-occluded conditions. At the end of 24 h, the cells were dismantled and the samples analyzed by either one of the following analytical methods.

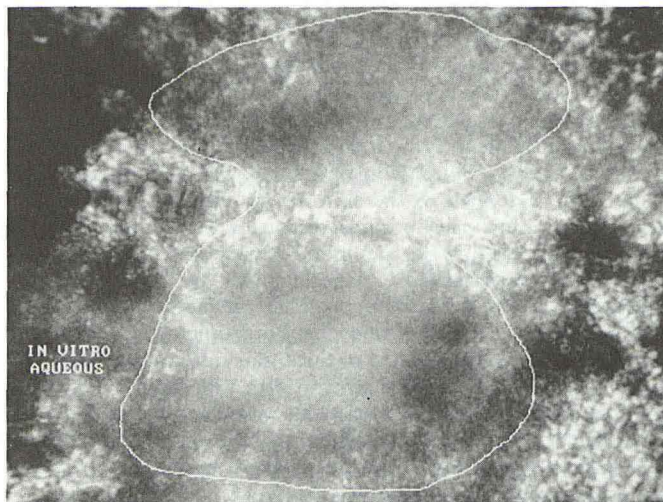
Quantitative Fluorescence Microscopy At the conclusion of the diffusion experiment, the skin was rinsed with 10 ml buffer, whereupon the epidermis was easily removed with forceps so as to prevent artificially high fluorescence of the pilosebaceous glands due to bound CF. An 8-mm diameter circular Keyes punch (Robbins Instruments, Inc., Chatam, NJ) was used to obtain a defined skin section. The ventral dermis, which was isolated after separating the dorsal membrane and scraping the cartilage via a method described by Matias and Orentreich [34], was mounted on a glass slide, dermal side up, and sealed using Gel-Mount.

The slide containing the hamster ear skin section was examined using a Leitz Fluovert FS microscope with an epifluorescence attachment and a silicon intensified target (SIT) 66 camera. Because carboxyfluorescein has an excitation wavelength of 490 nm and an emission wavelength of 520 nm, the glands were observed under blue light illumination: excitation waveband, 450–490 nm; emission, dichromatic mirror, 510 nm; and barrier filter, 520 nm. The glands were monitored using a 50 \times oil immersion lens. Care was taken to observe only the central portion of area of the ears exposed to treatment and the intensity of the fluorescent light was controlled electronically. The image of the gland under fluorescent as well as phase-contrast light illumination (for comparison purposes) was displayed via the SIT 66 camera on a television monitor with a VCR attachment. This image was then stored digitally in an IBM computer and the image processed using a Quantex QX-7 image processor. The processed image was then photographed and the fluorescence quantified. Autofluorescence from the sebaceous glands was minimal under the intensity used. A minimum of nine sebaceous glands in each skin section was monitored for fluorescence and the mean value was determined. Four such skin sections for each treatment formulation were analyzed.

Scraping Technique At the conclusion of the diffusion experiment, the diffusion cell was dismantled and the donor compartment rinsed with 5 ml buffer. The area of the ear exposed to treatment was then punched out with an 8-mm diameter circular punch, rinsed with 10 ml HEPES buffer, blotted with Kimwipe tissue paper to absorb excess formulation, and rinsed again with 5 ml buffer. The donor rinses, Kimwipe swab, and receiver solution were then assayed for CF using the fluorospectrophotometer. The whole ear membrane punched section was separated into the following compartments via either peeling or gentle scraping: epidermis, ventral dermis, cartilage, and dorsal (non-treated) side.

The sebaceous glands in the ventral dermis were removed using an intense scraping technique developed by Parthasarathy.* In this

* Parthasarathy S (personal communication, Orentreich Foundation for the Advancement of Science, Cold Spring, NY).



a

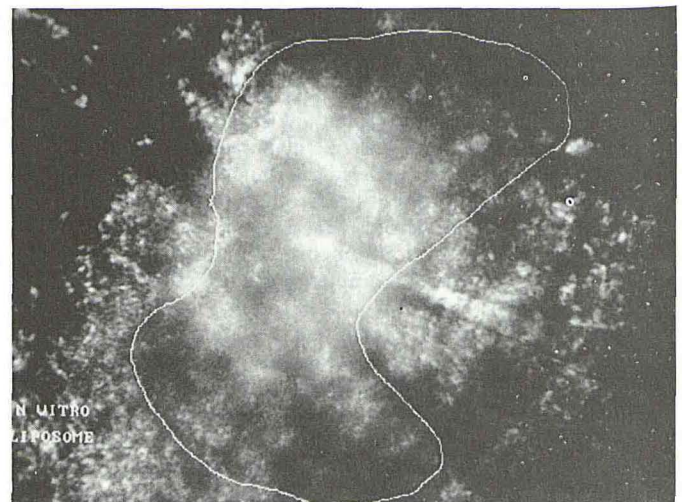


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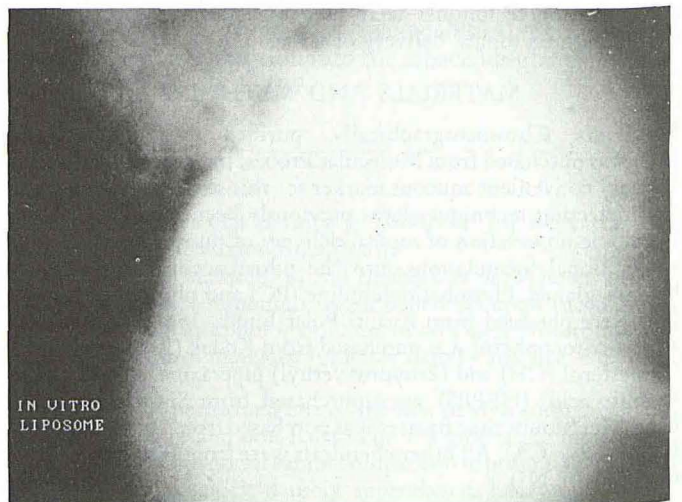


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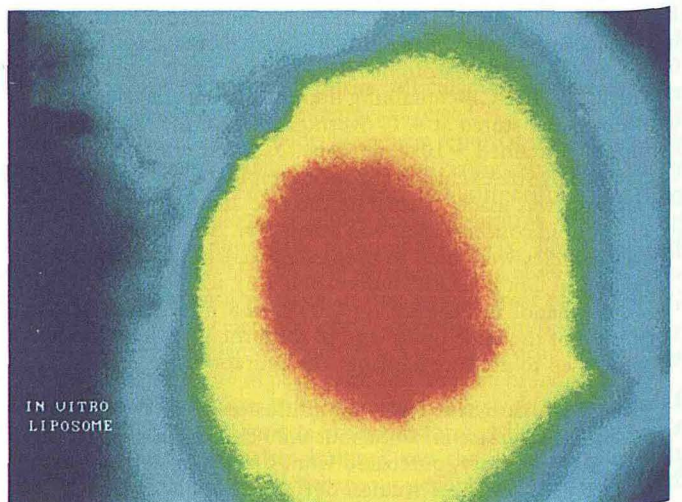
Figure 1. Representation of typical light (a), fluorescent (b), and computer color enhancement (c) images of hamster ear pilosebaceous units treated with aqueous CF. Sebaceous glands are outlined in the light image (a). Experimental details given in text.



a



b



c

Figure 2. Representation of typical light (a), fluorescent (b), and computer color enhancement (c) images of hamster ear pilosebaceous units treated with liposomal CF. Sebaceous glands are outlined in the light image (a). Experimental details given in text.

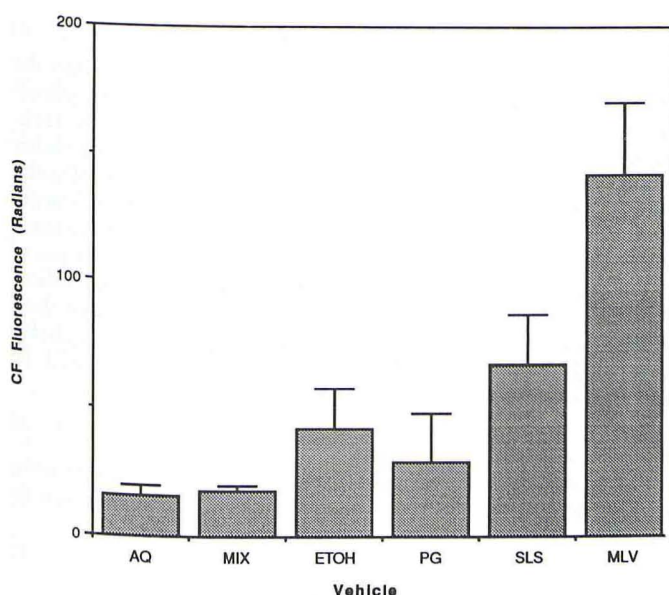
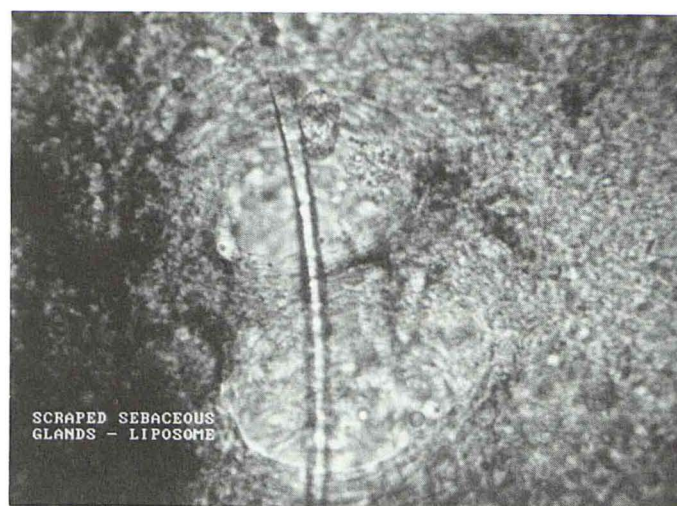


Figure 3. CF Fluorescence in hamster ear sebaceous glands using modified Franz diffusion cell technique as determined by quantitative fluorescence microscopy after 24 h topical application of 100 $\mu\text{g}/\text{ml}$ CF from various formulations. Bars, SEM; $n = 4$.

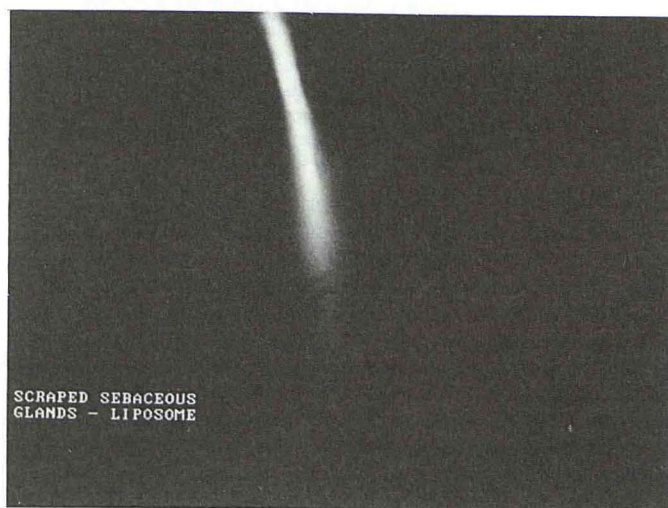
procedure, a dull scalpel was dragged across the underside of the ventral dermis. Care is taken to scrape with the minimum force necessary to dislodge the pilosebaceous material as evidenced by the appearance of a milky substance. The scraping procedure is considered complete when the areas of the ear previously occupied by the sebaceous glands appear as "holes" under light microscopy. This milky material (scraped glands) was collected and suspended in 10 ml buffer and sonicated for 5 min to disrupt membrane material so as to allow release of trapped CF. The preparation was stored overnight in a refrigerator and the solution was assayed for CF using the LS-5 fluorescence spectrometer. The technique was repeated in triplicate for each formulation treatment.

Data Analysis For the quantitative fluorescence microscopy, results were compared based on the mean and standard error of the average radians emitted from the pilosebaceous glands for the given treatment formulation. The glands were chosen at random in evenly spaced increments from the ventral ear membrane.

For the scraping technique, results were based on the comparison of the percent applied dose found in the various strata. Mean values and standard errors were determined for deposition in each tissue strata analyzed for each formulation tested. For both techniques, the results were normalized to the actual CF concentration applied based on fluorescence spectrophotometric analysis. Statistical comparisons for significance were performed by the independent *t* test method (one-paired).



a



b

Figure 4. Typical light (a) and fluorescent (b) images of hamster ear sections treated with liposomal CF after removal of the sebaceous glands. In many cases, the hair follicle remains embedded and is shown here for reference purposes. Experimental details given in text.

RESULTS

Figures 1a,b and 2a,b represent typical light (for reference purposes) and fluorescent images of pilosebaceous glands treated with aqueous CF and liposomal CF, respectively. Visual examination of color-enhanced images of these photos (Figs 1c and 2c) reveal the liposomal

Table I. Percent of CF Recovered in the Various Strata of Hamster Ear Following 24 h In Vitro Treatment with Different Formulations^a

| Compartment | Aqueous | Formulation Type | | |
|-------------------------|------------|------------------|-------------|------------|
| | | 5% PG | 0.05% SLS | MLV |
| Donor | 85.8 (2.8) | 87.1 (1.6) | 97.0 (1.8) | 66.8 (1.8) |
| Epidermis (ventral) | 3.9 (1.1) | 3.7 (0.6) | 2.9 (0.1) | 18.2 (7.0) |
| Cartilage | 0.2 (0.2) | 0.4 (0.1) | 0.4 (0.1) | 3.0 (2.5) |
| Dorsal (whole skin) | 0.1 (0.1) | 0.4 (0.2) | 0.3 (0.2) | 0.6 (0.1) |
| Pilosebaceous (ventral) | 0.1 (0.0) | 0.3 (0.1) | 0.4 (0.1) | 1.2 (0.3) |
| Dermis (ventral) | 0.1 (0.1) | 0.4 (0.1) | 0.5 (0.1) | 0.2 (0.1) |
| Mass balance | 90.3 (1.5) | 92.3 (1.2) | 101.7 (2.4) | 89.9 (3.7) |

^a The scraping method, as detailed in the text, was used to determine CF concentrations and the data are expressed as mean values (SE).

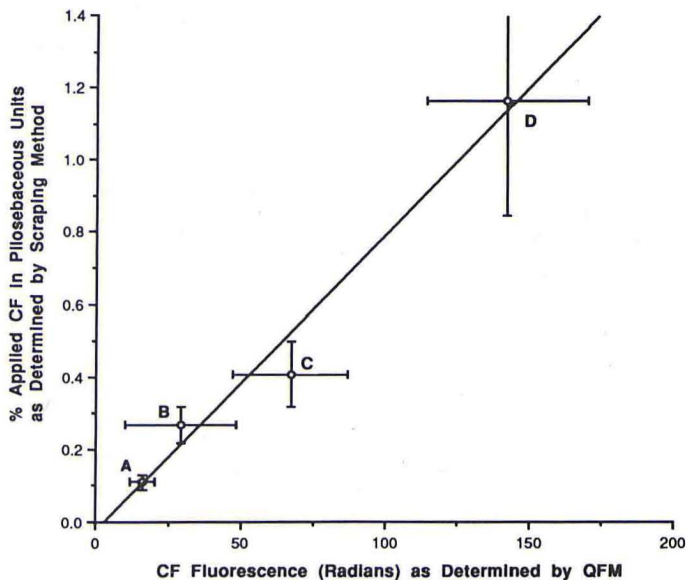


Figure 5. Comparison between percent CF deposited in pilosebaceous units as determined by the scraping technique and CF fluorescence as determined by quantitative fluorescence microscopy after 24 h topical application of 100 $\mu\text{g}/\text{ml}$ CF from various formulations. (A) aqueous solution; (B) 5% PG; (C) 0.05% SLS; (D) MLV.

CF-treated glands to have the most intense fluorescence located centrally along the piliary canal.

Figure 3 shows CF fluorescence in hamster ear sebaceous glands as detected by QFM after 24-h topical *in vitro* application of various formulations using the modified Franz diffusion cell technique ($n = 4$). The liposomal preparations tested showed an eightfold enhancement of fluorescence emission over both the aqueous solution and the phospholipid mixture. Both the ethanol and propylene glycol formulations exhibited about a twofold increase and the SLS formulation about a threefold enhancement over both the aqueous solution and the non-liposomal phospholipid mixture.

The deposition of CF from the liposomal formulation is greater than its deposition from any of the other vehicles tested ($p < 0.05$), even those formulations which, because of their solubility characteristics, would be expected to facilitate deposition of materials via the follicular route. The fact that the formulation containing the lipid mixture that was not processed into liposomes was ineffective is not surprising. Egbaria and Weiner [35] showed that whereas PC:CH:PS liposomes were effective in depositing cyclosporine into the skin, the same lipid composition used as an emulsifier in an emulsion formulation was essentially ineffective. They concluded that the lipids must be in a bilayer configuration in order to carry the drug into the skin.

Data from the scraping technique supports the findings of the quantitative fluorescence microscopic method (Table I). Figure 4a,b represent typical light and fluorescent images of liposomal CF-treated hamster ear section after removal of the pilosebaceous units. As can be seen from the photographs, the hair follicle itself remains embedded after removal of the sebaceous unit. Mass balance for this technique is relatively good because some loss of CF would be expected from protein binding. The amount of CF found in the pilosebaceous unit for that liposomal preparation was tenfold higher than for the aqueous solution and was again significantly greater than deposition from any of the other vehicles tested ($p < 0.05$).

There was excellent correlation ($r^2 = 0.97$) between QFM and the scraping technique (Fig 5) with respect to deposition of CF into the pilosebaceous units upon topical application of a variety of formulations, each containing $\approx 100 \mu\text{g}/\text{ml}$ CF. Although QFM is the more convenient of the two procedures, the scraping technique is far more versatile, as it is not limited to fluorescent markers.

DISCUSSION

In summary, carboxyfluorescein is selectively delivered into the hamster ear pilosebaceous unit (a model for the human pilosebaceous unit) as determined by two quantitative fluorescent techniques. Liposomal formulations are more efficient than any other vehicle tested for delivery of this marker through the follicular route. It should be pointed out that carboxyfluorescein is a negatively charged polar compound that penetrates the stratum corneum with great difficulty. Targeted follicular delivery via the use of liposomes would certainly be advantageous for a number of follicular diseases such as acne or alopecia. *In vivo* correlations of these results and the effect of liposomal entrapment of more hydrophobic compounds on delivery through the follicular route will be presented in a subsequent paper.

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